

ORIGINAL ARTICLE

Prevalence of coeliac disease in children and adolescents with type 1 diabetes mellitus in a clinic based population

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Background: Although the association between type 1 diabetes mellitus (T1DM) and coeliac disease is well known, the presenting features and clinical characteristics of the two diseases when they coexist are less well documented.

Methods: All patients with T1DM attending a paediatric diabetes clinic in London, UK, were screened for coeliac disease by serological testing for coeliac antibodies (antiendomysial and either/both tissue transglutaminase and antigliadin). Antibody positive patients were reviewed and their presenting symptoms, tissue biopsy result and coexisting morbidities investigated. Glycaemic control, growth and the effect of a gluten-free diet on these variables were also evaluated.

Results: Of the 113 patients with T1DM, 7 (6.2%) tested antibody positive. Jejunal biopsy confirmed coeliac disease in 5 of the 7 (4.4%) patients. Coeliac disease presented atypically or silently in the majority of cases with an unpredictable interval between diagnosis of diabetes and coeliac disease presentation. Coeliac disease did not appear to affect growth. Mean glycated haemoglobin (HbA1c) levels were not significantly raised in subjects (9.87%) compared with matched controls without coeliac disease (9.08%) ($p=0.249$). Analyses of the effect of a gluten-free diet on growth and HbA1c were limited. Of the seven subjects, two suffered other autoimmune diseases.

Conclusion: Coeliac disease presents atypically and unexpectedly in children and adolescents with T1DM. This, along with the strong association between the two diseases, supports the regular screening of coeliac disease among these patients. The value of a gluten-free diet cannot be commented on from this study alone although other studies show it reduces the risk of complications.

The association between type 1 diabetes mellitus (T1DM) and coeliac disease was observed as early as the late 1960s and has been noted in various studies since.^{1–3} This is unsurprising given that both conditions are strongly linked to the HLA system, in particular the haplotypes A1, B8, DR3 and DQ2.⁴ Coeliac disease and T1DM coexist more frequently than would be expected by chance and the prevalence of coeliac disease among patients with T1DM has been estimated as being between 1–10%. A large UK based study estimated the prevalence among children and adolescents to be 4.8%.⁵

Healthcare professionals face two challenges in caring for young people with coeliac disease and T1DM: firstly, the diagnosis of coeliac disease among a large number of patients who present asymptotically or atypically; and secondly, the prevention of the long term complications of coeliac disease. Given the increased prevalence of coeliac disease among diabetics, regular and repeated screening for coeliac autoantibodies has become a widely accepted practice. Symptomatic coeliac disease is only the “tip of the iceberg” and it has been recognised that coeliac disease is “more common and more varied in its presentation than previously thought”.⁵ The classical symptoms of failure to thrive, weight loss, steatorrhoea and a change in bowel habit are less commonly seen than milder or less specific symptoms (for example, recurrent abdominal pain).⁶

Coeliac disease is believed to have an adverse effect on T1DM, particularly with regards to glycaemic control. In addition, coeliac disease carries with it an increased risk of long term complications, including decreased bone density and gastrointestinal malignancies.^{7,8} Adherence to a gluten-free diet is difficult but appears to reduce the risk of malignancy.⁹ However, its effect on diabetes remains controversial.

This retrospective study aims to:

- estimate the prevalence of coeliac disease among a population of children and adolescents with T1DM within a clinical setting;
- investigate how coeliac disease presents among children and adolescents with T1DM in terms of its presentation and time course of development;
- investigate the effect of coeliac disease on the growth and glycaemic control of children and adolescents with T1DM and the benefit of a gluten free diet;
- examine the association of other diseases with coeliac disease and T1DM.

METHODS

Patients

The cohort included a population of 113 patients (58 males, 55 females), aged <19 years, with a diagnosis of T1DM who were currently attending the paediatric diabetes outpatient clinic at a large hospital situated in East London. The population comprised a large proportion of ethnic minorities, particularly from black and South Asian backgrounds. The study was approved by the hospital audit department.

Methods

From 2003, all patients were been screened for coeliac antibodies (tissue transglutaminase and antiendomysial) at least every 2 years or more frequently if they presented with symptoms suggestive of coeliac disease. Prior to 2003, serological screening involved antigliadin (IgA and IgG) and antiendomysial antibodies.

Abbreviations: HbA1c, glycated haemoglobin; T1DM, type 1 diabetes mellitus

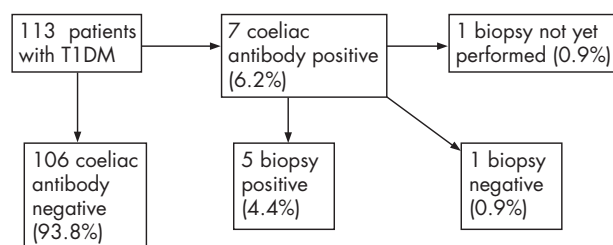


Figure 1 Study design.

Patients with a positive coeliac screen were recommended for an endoscopic gastroduodenal jejunal biopsy. Biopsies were examined histologically under a light microscope and the diagnosis of coeliac disease was based on the characteristic findings of subtotal or total villous atrophy, crypt hyperplasia and intraepithelial lymphocyte proliferation in the biopsy.

All patients with biopsy positive coeliac disease were advised to adopt a gluten-free diet. They were prescribed gluten-free products and received advice from a dietician.

Glycated haemoglobin (HbA1c) levels were taken as a long term measure of diabetic control.

HbA1c, height and weight data were obtained throughout the time each patient had been attending the clinic. Mean length of clinic attendance for the subject group was 60 months (range 16–116).

Controls

Levels of glycaemic control were analysed by comparing patients in the study group with control subjects. Control subjects were patients included in the initial cohort who also had a diagnosis of T1DM (but not coeliac disease) and who were age and sex matched.

RESULTS

Prevalence

Figure 1 shows that of the 113 patients screened, 106 were coeliac screen negative and seven were coeliac screen positive (6.2%). These seven patients (two males, five females) formed the study group. Of these seven patients, six underwent jejunal biopsy. Five of the six biopsied patients were classified as biopsy positive (4.4%). The mean age of the subject group was 12.1 years (range 6.5–17.2).

Onset of disease

The development of coeliac disease in patients with T1DM does not appear to follow a predictable course. On average, subjects developed coeliac antibodies at 33.8 months following diagnosis (approximately 2 years 10 months). However, this value varied greatly between patients (fig 2). In our study, three of the seven subjects developed coeliac antibodies within one year of developing diabetes while two developed antibodies after an interval of more than 5 years.

Four of the five biopsy positive patients yielded a positive biopsy immediately. One did not, developing coeliac antibodies approximately 5 years after being diagnosed with diabetes. He was biopsied twice, the first time soon after the positive coeliac screen but was negative for coeliac disease. However, a subsequent biopsy 3 years later was diagnostic for coeliac disease.

Symptoms

There does not appear to be a strong correlation between the classical “coeliac symptoms” and a positive biopsy result (table 1). Symptoms suggestive of coeliac disease are mild, non-specific and often vague in patients with diabetes. Common symptoms among the study group included recurrent abdominal pain (five patients), weight loss (two patients) and frequent hypoglycaemic episodes (three patients). In addition, the presence of symptoms is often noted only retrospectively, after a diagnosis of coeliac disease has already been made. One patient had a positive biopsy for coeliac disease despite having been completely asymptomatic while another had symptoms which might be considered typical of coeliac disease (weight loss and altered bowel habit) but was found to have a negative biopsy result.

Growth

Height and weight data were obtained from case notes and plotted on growth charts. Average height and weight standard deviation scores (SDs) were calculated from data collected throughout the time they had been attending the diabetes clinic (table 2).

Subjects showed satisfactory growth in terms of both height and weight. Mean height and weight SDs did not deviate significantly from expected values. In height, mean SDs ranged from -0.69 to 1.46 standard deviations from the mean while weight SDs ranged from -0.33 to 1.57 standard deviations from the mean.

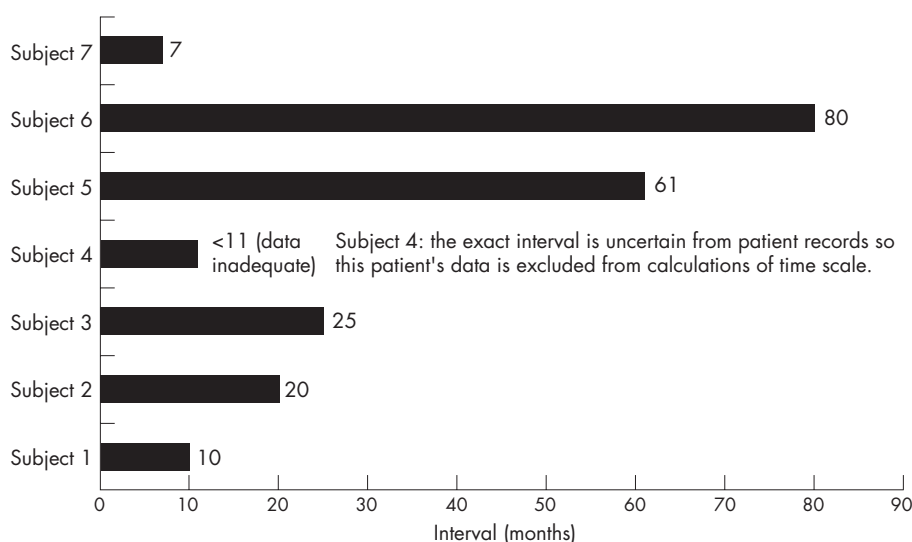


Figure 2 Interval between diagnosis of type 1 diabetes mellitus and development of coeliac antibodies.

Table 1 Patient characteristics of the study group

Subject No	Age (y)	Antibodies positive	Biopsy result	Coeliac symptoms
1	6.5	EMA, TTG	Positive	None
2	17.0	AGA, EMA, TTG	Positive	Weight loss, abdominal pain
3	12.4	AGA, EMA	Positive	Abdominal pain
4	10.8	AGA, EMA	Positive	Abdominal pain, recurrent hypoglycaemia
5	14.2	AGA, EMA TTG	Positive	Abdominal pain, recurrent hypoglycaemia, weight loss, abdominal distension, offensive smelling stools
6	17.2	AGA, EMA TTG	Negative	Weight loss, recurrent hypoglycaemia, increased bowel motions
7	6.5	EMA, TTG	Not done yet	Abdominal pain, recurrent hypoglycaemia

AGA, antigliadin antibodies (IgA and IgG); EMA, antiendomysial antibodies; TTG, tissue transglutaminase antibodies.

All subjects showed a stable growth pattern, following the centile curves in a predictable fashion. This was also the case with weight, apart from in two subjects, one of whom suffered from an eating disorder. This patient (subject No 2) adhered poorly to her treatment for both diabetes and coeliac disease. For this reason, we have excluded her data from our analyses of glycaemic control and the effect of a gluten-free diet to prevent it from misleading our analyses.

Glycaemic control

Glycated haemoglobin (HbA1c) values were obtained from case notes and compared to the HbA1c values of matched diabetic controls (table 3).

The higher mean HbA1c in subjects (9.87) compared with controls (9.08) was analysed using the Wilcoxon rank sum test. This showed that there was no significant difference between the subject and control groups ($Z = -1.153$, $p = 0.249$).

Effect of treatment

Our evaluation of the effect of treating coeliac disease with a gluten-free diet was severely limited. Only one patient had sufficient pretreatment and post-treatment data. Reasons for this lack of data included non-adherence to a gluten-free diet and limited pretreatment data in two patients who had previously lived abroad.

Associations

Apart from coeliac disease and diabetes, several patients in the study group were affected by other medical conditions believed to have an association.² Two of the seven subjects had autoimmune thyroid disease—one with hypothyroidism and the other with thyrotoxicosis. Another of the patients suffered from severe asthma.

DISCUSSION

Of a total of 113 patients in our cohort, we detected seven antibody positive cases (6.2%) of whom at least five had biopsy

changes consistent with coeliac disease. One antibody positive patient has yet to have a biopsy, which means that the estimated prevalence of coeliac disease among children and adolescents with diabetes in our clinical setting is at least 4.4%. This prevalence rate is consistent with previously estimated values and is reflective of the association between the two diseases. The relatively high prevalence rate supports the practice of screening patients with T1DM for coeliac disease.¹⁰

The time scale of developing coeliac disease following the development of T1DM is unpredictable and varied from approximately 7 to 80 months between different patients. Seroconversion of coeliac autoantibodies in patients previously negative for autoantibodies suggests that screening must be carried out regularly and repeatedly. Even if a patient has tested negative for coeliac antibodies in the past this does not mean they will not develop the disease in the future. The profile of subject No 6 suggests that the features of coeliac disease may develop gradually over time. Six years after the diagnosis of diabetes, he tested weakly positive for antiendomysial antibodies but negative for antigliadin antibodies. Subsequently however, he became strongly positive for antiendomysial and tissue transglutaminase antibodies alongside the development of symptoms such as weight loss, poor glycaemic control and increased bowel motions. His jejunal biopsy was “slightly suboptimal but essentially normal” and may suggest an evolving condition.

Of the five patients with biopsy positive coeliac disease, only one presented with “classical symptoms”, including diarrhoea, offensive smelling stools and abdominal distension. Of the others, one was asymptomatic and three presented atypically/silently, with their main symptom being recurrent abdominal pain. The presence of symptoms does not appear to correlate with a positive biopsy result in patients with a positive coeliac screen and symptoms are often mild and vague such that they are only noted retrospective to positive coeliac testing. This means that a diagnosis of coeliac disease cannot be based on symptoms or serological tests alone without a definitive small bowel biopsy. Our study supports the theory that symptomatic coeliac disease may be just the “tip of the iceberg” and that there is a spectrum of gluten sensitivity. Screening allows us to detect the atypical, asymptomatic and silent presentations of coeliac disease which may be beneficial in that the risk of potential complications can be reduced by early treatment.

A recognised symptom of coeliac disease is failure to thrive and weight loss, and we might therefore expect to see impaired growth in subjects with coeliac disease. However, we did not see evidence of this in our study group. This may be because many of our patients were diagnosed with coeliac disease early in the progression of the disease, before the overt symptoms of weight loss and failure to thrive could be seen. Also, a high index of suspicion for coeliac disease in diabetic patients means that subjects who present with weight loss are screened and

Table 2 Height and weight data for the study group

Subject No	Average height SDs	Average weight SDs
1	1.27	0.87
2	-0.35	-0.33
3	0.96	1.57
4	-0.69	0.09
5	-0.11	0.40
6	1.46	0.71
7	0.86	0.99
Group mean	0.48	0.61

Table 3 Glycated haemoglobin levels in patients and controls

Subject No	Glycated haemoglobin	Control No	Glycated haemoglobin
1	8.8 (7.7–9.9)	1	8.3 (7.8–9.4)
2*	14.0 (10.7–17.8)	2*	8.9 (7.1–12.1)
3	10.6 (9.2–11.6)	3	10.7 (8.8–12.1)
4	9.5 (7.9–10.6)	4	8.6 (5.7–10.3)
5	12.3 (7.7–13.4)	5	8.6 (6.7–10.5)
6	9.8 (9.2–12.4)	6	9.3 (7.2–11.1)
7	8.2 (6.7–8.8)	7	9.0 (7.6–10.6)
Subject mean	9.87	Control mean	9.08

Values are mean (range) %.

*Data from subject No 2 were excluded from analyses for reasons described under the section "growth".

treated before this weight loss has had time to become significant and malabsorption has had time to affect linear growth. In one patient, we saw evidence of increased growth in terms of height following the introduction of a gluten-free diet. Larger studies may provide evidence in support of this observation.¹¹

Glycaemic control, as measured by HbA1c levels, did not differ significantly between subjects and controls. It has been postulated that patients with coeliac disease as well as T1DM may have poorer glycaemic control than patients with T1DM alone but we did not find this to be the case in our data. The reason for this may be that patients with coexisting coeliac disease and diabetes, although more likely to suffer from poor control of their diabetes (raising HbA1c), are also more likely to suffer from hypoglycaemia (lowering HbA1c) perhaps as a consequence of a degree of malabsorption. This can therefore result in lower HbA1c levels than might be expected and a non-significant difference between subjects and controls. In addition, the large proportion of silent or asymptomatic cases may mean that the intestinal mucosa has not been damaged sufficiently to cause symptoms of malabsorption.

Evaluating the effect of a gluten-free diet was difficult, primarily because patients find it difficult to adhere to this strict diet. Thus we could not evaluate the effect of gluten-free dietary therapy on growth or HbA1c levels. Some studies have shown there to be no significant changes to HbA1c with a gluten-free diet.^{5 12–15}

We had hoped to be able to investigate a trend we had observed towards more stabilised HbA1c levels following treatment but our analyses were limited by lack of data. Our hypothesis is that HbA1c levels are more stable following gluten-free treatment because of the reduction in the number of hypoglycaemic episodes and therefore the corresponding hyperglycaemia that follows over-treatment of the hypoglycaemia.

Finally, the observation that two of our T1DM patients with positive coeliac antibodies also suffered from autoimmune thyroid disease is in line with the association described between coeliac disease and autoimmune diseases. Collin *et al* found that 5.4% of patients with coeliac disease also had type 1 diabetes compared with 1.5% of controls, and that 5.4% of patients with coeliac disease also had autoimmune thyroid disease compared with 2.7% of controls.² Coeliac disease is also associated with asthma; one of our subjects suffered from severe asthma. There is reason to have a high index of suspicion for coeliac disease in patients with T1DM who suffer from other autoimmune diseases or associated diseases and vice versa. Current practice is to screen all patients attending the diabetic clinic for thyroid antibodies and coeliac antibodies.

This study has found that the prevalence of coeliac disease among a paediatric population with T1DM is high (at least

4.4%). In addition, the unreliability of investigating patients for coeliac disease based purely on the presence or absence of symptoms supports the practice of regular screening. Repeated screening is also crucial as a negative coeliac screen does not exclude the possibility of developing coeliac disease in the future.¹⁶ A gluten-free diet is the treatment of choice for coeliac disease but patients with diabetes find it especially difficult to adhere to treatment. Coping with a second chronic disease can be very demanding on patients and their families. Also, the dependence of diabetic patients in the West on gluten-containing carbohydrates such as bread and pasta makes it difficult to avoid such products. Furthermore, as many of the patients with coeliac disease and diabetes do not suffer overt symptoms, they may lack the motivation to adhere to treatment.

There is evidence that strict gluten restriction reverses or at least reduces the risk of complications from coeliac disease, in particular the risk of malignancy.⁹ There has been controversy about whether or not it is worth diagnosing and treating subclinical coeliac disease but it appears that the risk of developing complications exists regardless of the severity of symptoms. Malignancy may be the first presentation of subclinical coeliac disease and osteoporosis is a well recognised complication, regardless of symptoms.^{7 17} Some studies have shown a significant increase in height with a strict gluten-free diet.¹¹

CONCLUSION

We have found evidence to support the current practice of screening for coeliac disease among paediatric patients with T1DM. Our findings support the theory that there exists a spectrum of gluten insensitivity. Height, weight and HbA1c levels do not seem adversely affected by coeliac disease. However, from the results of other studies, a gluten-free diet may still be important in reducing the likelihood of malignant complications.

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FILLER.....

Medical numeracy

Doctors are notoriously poor at mathematics, but one of the more difficult questions they have to answer is how many people it takes to make a medical consultation. The easy short answer is two (doctor and patient), but this simplistic reply will not do. A gofer is needed to make the clinic run smoothly; a chaperone is necessary when patients are to be examined; and an interpreter if there is more of a language problem than medical jargon. These three roles can often be combined by an energetic nurse, but three is probably the minimum number with which outpatient sessions can be conducted. However, this is only part of the answer.

Patients have a right to be accompanied by a friend or relative, and it is now usual for them to enter the consulting room with at least one person (not usually introduced) in tow. In school holidays, the next generation is often included in the trip too. This can lead to some overcrowding problems. I once had to ask four adult relatives who had decided to line the wall of the office to select two accompanying persons who could sit down in a civilised manner. Not least of the problem is that relatives often contradict the patient and each other, creating an unfunny comedy, which does not lead to effective diagnosis and management. The more there are of them, the worse it gets.

Nowadays we also have specialist nurses who perform a useful liaison and progress-chasing service. They may run their own clinics, but often sit in with doctors seeing patients, adding further to the throng. This has got a bit out of hand, and can be a little counterproductive as the dynamics of the doctor's office have shifted and this diverts attention from the main point, the patient's defective health.

Could we call a truce and ask for a ceiling on the numbers involved and in the room, like five? This could only be an improvement, no least in controlling the temperatures of what are generally overheated rooms, which are not improved by excessive numbers of human beings.

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